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Hypercalcemia in Chronic Lymphatic Leukemia Patients

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INTRODUCTION

Hypercalcemia is a well-known complication of many malignancies [1]. Several lymphoplasmocytic dyscrasias, such as multiple myeloma, lymphoma, and adult T-cell lymphoma-leukemia, are known to be accompanied by hypercalcemia. Yet the combination of hypercalcemia with chronic lymphatic leukemia (CLL) is not well-characterized.

Our literature review revealed only a few case reports in which the mechanism of hypercalcemia was either hyperparathyroidism [2] or cryptogenic [3]. The purpose of this study was to evaluate the incidence of hypercalcemia in CLL and to determine the clinical significance of this finding.

PATIENTS AND METHODS

We screened retrospectively a group of 1,200 patients from computerized diagnostic lists of all Kupat-Holim sick fund hospitals between 1974–1991 in whom B-CLL was diagnosed. The criteria for diagnosis of CLL were: 1) sustained and absolute lymphocytosis of more than 10×10^3/l, most of the cells being mature-appearing lymphocytes; 2) a bone-marrow aspirate showing >30% lymphocytes among all nucleated cells; and 3) a majority of peripheral blood lymphocytes with B-cell markers.

Patients with hairy-cell leukemia, prolymphocytic leukemia, Waldenström[1], macroglobulinemia, and other subtypes of lymphoma and leukemia, as well as other solid neoplasias, were excluded except for patient 7, who suffered from localized squamous-cell carcinoma and basal-cell carcinoma of the skin. The disease was staged according to the Rai staging system [4] at presentation and at diagnosis of hypercalcemia. Hypercalcemia was defined as calcium levels >10.5 mg/dl in at least three determinations.

RESULTS

Out of 1,200 B-CLL patients evaluated, 7 CLL patients with hypercalcemia were found in the present survey. The features of these patients are summarized in Table I. None of them was treated by drugs known to cause hypercalcemia, except for patient 6, who was treated by oral calcium for osteoporosis. All other patients were treated by corticosteroids. Additional treatments included cyclophosphamide, vincristine, chlorambucil, etoposide (VP16), and radiotherapy in various combinations (Table I).

Hypercalcemia was diagnosed after a mean period of 4.14 years following diagnosis of CLL. Most patients were in advanced stages (3–4) at time of hypercalcemia, except for a single patient in stage 2.

Definitely increased levels of parathyroid hormone (PTH) were detected in patients 2 and 3. Patient 5 had a level of PTH within normal range, but this value was elevated relative to serum calcium levels. Patients 2 and 5 had nephrolithiasis. No further investigation was devoted to locating or identifying the source of PTH among these patients.

The patients with inappropriately high levels of PTH were characterized by a relatively indolent course of CLL and a prolonged survival ranging from 9–10 years (patients 2, 3, and 5). Patient 4 had no evidence of hyperparathyroidism. He died while the diagnosis of hypercalcemia was being made and 4 years after the primary diagnosis of CLL. Patient 6 had depressed levels of PTH as well, and yet had a relatively benign course of the disease after diagnosis of hypercalcemia. Her hypercalcemia could

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have been related to calcium preparation that she had consumed. Patient 7 had a florid course of disease. He died 3 months after diagnosis of hypercalcemia. All patients died of systemic infections.

DISCUSSION

Our study confirms the rarity of the association between B-CLL and hypercalcemia relative to its higher prevalence in other hematologic malignancies such as multiple myeloma (about 33%) or adult T-cell leukemia (about 66%) [6]. Three of our patients with hypercalcemia and B-CLL had inappropriately increased levels of parathyroid hormone, implying the presence of primary hyperparathyroidism, though in neither case had any further investigation toward establishing the diagnosis been made. Thus, we cannot completely rule out the possibility of PTHrP as the cause of hypercalcemia in these patients (some of whom were diagnosed in the era when the ability of laboratory kits to differentiate between PTH and PTHrP was poor). In the other cases, laboratory data suggest that hypercalcemia was caused by a nonparathyroid neoplasia probably related to B-CLL. Though patient 7 had additional malignancies, i.e., localized squamous-cell carcinoma and basal-cell carcinoma of the skin, we believe that the hypercalcemia was associated with CLL, since it was part of a severe flare-up of the hematological disease. Among the rest of the patients, other malignancies associated with hypercalcemia were not identified. In patient 6, the consumption of calcium preparation could have contributed to hypercalcemia.

Malignancy-associated hypercalcemia may be divided into three major categories: humoral hypercalcemia mediated by parathyroid hormone-related protein (PTHrP), hypercalcemia induced by dysregulated production of calcitriol, and local osteolytic hypercalcemia in which there is activation of osteoclasts in the vicinity of tumor cells in bones [6]. Several mechanisms for hypercalcemia in CLL have been suggested. Some patients have had hypercalcemia as a consequence of the coincidental presence of hyperparathyroidism [7,8]. Among other cases described, the mechanism of hypercalcemia was unclear and was attributed to increased osteoclastic activity [9] or transformation of the CLL to prolymphocytic leukemia [10].

We suggest that the presence of primary hyperparathyroidism as the cause of hypercalcemia does not significantly affect patients' survival.

Among patients without elevated levels of PTH, hypercalcemia seems to herald a terminal stage of the disease.

We recommend performing a prospective follow-up and investigation of this unique cohort of patients with CLL, to identify the source of hypercalcemia and its impact on prognosis.

TABLE I. Clinical Characteristics of B-CLL Patients With Hypercalcemia*

Patient no.	Age (sex)	Stage at diagnosis	WBC × 10^3/l (total lymphocytes)	Time from diagnosis to hypercalcemia (years)	Stage at hypercalcemia	Calcium (mg/dl)	PTH (normal range, 10–65 pg/ml)	X-ray or bone scan findings	Treatment	Cause of death	Survival since diagnosis of CLL (years)	Survival since diagnosis of hypercalcemia (months)
1	69 (M)	2	70 (42)	3	2	11.2	N.D.	N.D.	C	Septicemia	4	12
2	63 (F)	2	15 (11.6)	2	4	11.7	140	Pathological fracture of vertebrae	C, P, Cy	Septicemia	10	96
3	55 (F)	2	14 (13)	9	4	14	330	Normal scan	P, Cy, VP-16	Septicemia	9	8
4	53 (M)	4	9.3 (4.6)	4	4	13.8	<1	Pathological uptake in ribs	P, C	Septicemia	4	0.5
5	56 (M)	2	14 (8)	9	4	13.2	49	Osteopenia	P	Septicemia	9	0.5
6	51 (F)	2	99 (93)	8	3	12.4	3.3	Pathological fracture	P, C, R	Septicemia Fungal infection	9	12
7	61 (M)	2B	160 (115)	2	4	16.9	N.D.	N.D.	P, C, V, leukopheresis	Pneumonia	2	3

*C, chlorambucil; P, prednisone; Cy, cyclophosphamide; V, vincristine; R, radiotherapy; N.D., not done.

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